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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,598	09/20/1999	MASAHIKO MIHARA	350292000800	4167

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,598	MIHARA, MASAHIKO	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22, 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 14-22, 33-38 are pending and under consideration.

The Appeal Brief filed on 8/16/2004 has been entered. However, upon further consideration, PROSECUTION IS HEREBY REOPENED, and a new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2). This is a non-final action.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-22, 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for while being enabling for specific anti-IL-6 receptor monoclonal antibodies (PM-1 and MR16-1) as therapeutic agents for diseases involving IL-6, does not reasonably provide enablement for a method of treating multiple sclerosis.

The claims are directed to methods of treatment of, *inter alia*, multiple sclerosis. Art recognized methods of treatment of multiple sclerosis are set forth in the Merck Manual (page 1476). The Merck Manual shows that methods of treating multiple sclerosis with the claimed anti-IL-6 receptor monoclonal antibodies are not art recognized, and that absent *in vivo* clinical data it would require undue experimentation to practice this method of treating multiple sclerosis in humans.

The CAFC decision (Genentech Inc. v. Novo Nordisk, 42 USPQ2d 1001, 1997) expressly states that:

> "When there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Here, given the breadth of claims 14-22, 33 in light of the predictability of the art as determined by the number

of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of skill in the art to practice the claimed invention. In the Reply filed 3/4/2002, Applicant presented several pieces of data indicating that the anti-IL-6 receptor antibody was efficacious in a mouse EAE model. At that time the rejection under 35 USC 112 first paragraph was withdrawn. However, after further consideration, the Examiner has determined that this data needs to be presented in a 1.132 Declaration, since the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) (MPEP § 2145).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-22, 33-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gijbels et al (1995) in view of Vink et al. (1990), and further in view of U.S. Patent No. 5,605,930 (Samid) for reasons of record set forth in the Office Action of 3/11/2003.

Gijbels et al. teaches the administration of antibodies to IL-6 in the EAE model of multiple sclerosis (page 799, Table I). The administration of the mAB to IL-6 significantly reduced the development of EAE, both in actively induced EAE and in the adoptive transfer model of EAE. Gijbels does not disclose administration of antibodies to IL-6 receptor. Vink et al. teaches the administration of anti-IL-6 receptor antibodies (page 998, second column, third

paragraph) as well as antibodies to IL-6 (page 998, Figure 1). These antibodies both block the action of IL-6 (page 998, column 2, third paragraph). Given the teaching of Gijbels of the beneficial effect of blocking the effect of IL-6 in the EAE model, along with the teaching of Vink that the effect of IL-6 can be neutralized by antibodies to both IL-6 and IL-6 receptor, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of administration of anti-IL-6 receptor antibodies to treat MS. The motivation is provided by Gijbels who concludes that the protective effect of anti-IL-6 in EAE might have therapeutic effect in inflammatory conditions of the CNS, including MS (page 804).

Applicant argues that the combination of references fails to teach or suggest the claimed methods. Applicant argues that the primary document Gijbels provides no indication that administering an antibody directed to lL-6 receptor could be used to treat a sensitized T-cell disorder. However, Gijbels teaches that the protective effects of anti-IL-6 have been described in several in vivo models of autoimmune or inflammatory conditions, and that the conclusion from these studies is that antibodies to IL-6 are protective by neutralizing IL-6 activity (page 801, column 1, first full paragraph), and that the efficacy of the neutralizing effect of anti-IL-6 antibodies is shown in Figure 1(a) (Gijbels at 798). Since antibodies to IL-6 receptors would also neutralize IL-6 activity, these antibodies would be expected to function to treat an IL-6 mediated disease, since the effect, i.e. the neutralization of IL-6 activity, is the same (see Abstract, page 795). Applicant further argues Gijbels could not predict how the IL-6 directed antibody performed its function, and cites page 795 which states that the disease-reducing effect of the anti-lL-6 antibodies could be caused by neutralization of IL-6 activity or by enhancement of IL-6 activity via induction of higher IL-6 levels in the CNS. However, according to Gijbels

there are only two ways the antibodies are active, one of which is by neutralizing IL-6 activity. Since anti-IL6 receptor antibodies would be expected to neutralize IL-6 activity, there is a 50% probability that these antibodies would be effective, thus meeting the standard of a reasonable expectation of success.

Applicant further argues that Vink also does not indicate a T-cell mediated disorder could be treated with an antibody that neutralizes IL-6, and teaches away from interchanging an antibody directed to lL-6 with an antibody directed to IL-6 receptor. However, Vink teaches that both antibodies to IL-6 and IL-6 receptor are capable of neutralizing the plasmacytoma growth factor activity of IL-6, thereby inhibiting tumor formation (Vink at 998, column 2, third paragraph). Furthermore, the anti-IL-6 receptor antibody is known to bind to cells expressing IL-6 receptor and compete with IL-6 for binding, an indication that the antibody is blocking IL-6 activity, by binding the receptor, which is the same activity that the antibodies of the instant application possess (Specification at 35, lines 23-26).

Applicant also argues that Samid fails to teach or suggest IL-6 is involved in the sensitized T-cell mediated diseases, and highlights unpredictability for therapeutics targeting the molecule, and argues that Samid, however, fails to teach that lL-6 expression is involved with the pathogenesis and/or symptoms of a T-cell-mediated diseases let alone a sensitized T-cell mediated disease. However, Samid discloses that IL-6, is a pleiotropic cytokine that plays a central role in defense mechanisms, including the immune-response, acute phase reaction and hematopoiesis. Samid further discloses that abnormal expression of the IL-6 gene has been suggested to be involved in the pathogenesis and/or symptoms of a variety of diseases, including non-malignant disorders associated with abnormal differentiation programs, autoimmunity and

inflammatory processes, e.g., uveitis (column 66, lines 20-47). Given the disclosure of Samid of the central role that IL-6 plays in inflammatory processes, it would be an expected property of the method of administration of anti-IL-6 receptor antibodies to treat MS, that this method of administration would treat other autoimmune and inflammatory processes, such as uveitis, thyroiditis, dermatitis and hypersensitivity.

Applicant further argues that given the unpredictability of treating sensitized T-cell disorders with an anti-IL-6 receptor antibody, there was no reasonable expectation for successfully performing the claimed methods. However, as set forth above, the Gijbels reference gives two possibilities for the are only two ways the antibodies are active, one of which is by neutralizing IL-6 activity. Since anti-IL6 receptor antibodies would be expected to neutralize IL-6 activity, there is a 50% probability that these antibodies would be effective, thus meeting the standard of a reasonable expectation of success.

Applicant further argues that there is no motivation to combine the references, however, the Vink reference shows that antibodies to IL-6 and IL-6 receptor have similar effects when administered, by blocking IL-6 activity, while the Gijbels reference teaches the efficacy of anti-IL-6 activity therapy in the EAE model of MS.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 27, 2004

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